REMARKS

The Office Actin and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 19, 21-23, 25, 28, 31-36, 40, 41, 43-45, 48, 50, 53-55 and 57-62 presently appear in this application, with claims 33-36 being withdrawn by the examiner, and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 23, 40, 48 and 61 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated by the amendment to claims 1 and 40 to replace the language "includes" with "comprises".

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 19, 21-23, 25, 28, 31, 32, 40, 41, 43-46, 48, 50, 53-55 and 57-62 have been rejected under 35 U.S.C. §112, first paragraph, because the examiner states that the specification, while being enabling for a method of inducing proliferation of hepatocytes in CCL_4 induced chemical cirrhosis, does not reasonably provide enablement for a method for treating liver cirrhosis as recited in claim 19. This rejection is respectfully traversed.

A copy of Huang et al., *World J. Gastroenterol.* 12(9):1386-1391 (2000), is attached hereto as evidence that liver cirrhosis, as the final stage of hepatic fibrosis caused by various liver insults and characterized by widespread fibrous scarring, is the same regardless of causes and involves abnormal accumulation of extracellular matrix (ECM) components, particularly collagen (see lines 1-8 of the "Introduction" on page 1386). Huang used the art accepted CCl_4-induced rat model of liver cirrhosis to study the therapeutic effect of IL-10 on liver cirrhosis/hepatic fibrosis.

It would be clear to one of ordinary skill in the art based on the wealth of knowledge on liver cirrhosis and the CCl_4 model that finding a treatment for liver cirrhosis is different from preventing liver cirrhosis because, while there may be differences in preventative effects depending on how liver cirrhosis is induced, the treatment, as presently claimed, does not cure how liver cirrhosis is induced but rather treats the hepatic fibrosis (fibrous scarring) seen in liver cirrhosis. Once liver cirrhosis is present, it is not unexpected that treatment for liver cirrhosis will be equally effective regardless of the cause. That is the basis for the countless studies in the art using the well accepted CCl_4-induced rat model

of liver cirrhosis. Such numerous studies on treatment using the CCl_4 model are certainly not directed to treating only CCl_4-induced liver cirrhosis but rather to treat liver cirrhosis in general, as would be recognized and understood by those of skill in the art.

For example, an alcohol dehydrogenase or the like may prevent alcohol-induced cirrhosis by detoxifying the alcohol before it reaches the liver. While a method of using alcohol dehydrogenase may prevent specifically induced liver cirrhosis, it will not however treat cirrhosis after it occurs, nor will it prevent any other cause of cirrhosis. The examiner provides no scientific basis in the literature or solid reasoning which would cause one to believe that the treatment of liver cirrhosis, on the basis of the well accepted CCl_4 model, will not be effective to treat cirrhosis regardless of cause. Claims 59-62 are directed to cirrhosis caused by hepatotoxic agents, for which the examiner gives no scientific reasoning at all in rejecting these claims. The decision in *In re Marzocchi,* 169 USPQ 367 (CCPA 1971), states:

> In the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a broad statement put forward as enabling support for a claim; this

> will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles; … it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement; otherwise, there would be no need for the applicant to support his presumptively accurate disclosure.

The examiner has not satisfied her burden of rebutting applicants' presumptively accurate disclosure.

Furthermore, applicants do not understand how the examiner construes applicants' arguments as arguing on the record that CCl_4-induced cirrhosis is disparate from Jo-2 mAb induced liver injury and hepatocyte apoptosis and therefore the factors causing liver cirrhosis <u>are pertinent in the treatment of liver cirrhosis</u> by IL-6. Applicants' previous arguments and the statements made in the Dreano 1.132 declaration in the context of §103(a) do not contradict applicants' arguments against this enablement rejection because a reference to <u>prevention</u> of apoptosis caused by Jo-2 mAb would not suggest that one could <u>prevent</u> CCl_4-induced cirrhosis.

Finally, with regard to the examiner's last statement in this rejection that the 1.132 declaration is not based on

results or data relevant to "all the defects recited in the claims" and is of little probative value for the claimed method of treating liver cirrhosis by administering an effective dose of IL-6, the only defect recited in the claims is liver cirrhosis. What the Dreano 1.132 declaration provides is a showing that a pre-treatment effect, such as observed by Kovalovich, cannot reasonably predict the post-treatment effect and vice versa.

Accordingly, the present claims are fully enabled by the present specification to one of skill in the art.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 19, 21-23, 25, 28, 31, 32, 40, 41, 43-45, 48, 50, 53-55 and 57-62 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Kovalovich et al. (2000). This rejection is respectfully traversed.

The Dreano 1.132 declaration provides evidence in the art as to why there is no reasonable predictability or expectation in general that what works in pre-treatment (protective effect) will work in treatment (therapeutic effect). Thus, because there is no reasonable predictability (or expectation of success), the presently claimed invention is not obvious according to the obviousness rationales from the *KSR v.*

Teleflex decision. The examiner's dismissal of the declaration is not on point. Applicants are not trying to prove unexpected results to rebut the obviousness rejection. Rather, applicants are providing a showing that the examiner has not established a *prima facie* case of obviousness. There is simply no reasonable predictability that a showing of prevention, in general, will extrapolate into a showing of effectiveness for treatment. For other indications and compounds generally, if it is hit or miss as to whether or not pre-treatment with a given substance has a protective effect and treatment would also have a therapeutic effect as well, then how can the examiner contend that there is reasonable predictability, especially at a recited dose (0.1 to 10 mcg/kg weight) that is 100 to 1000 fold less than the dose used in Kovalovich.

While it may be obvious to try doses around 1000 g/kg (mcg/g) as used in Kovalovich, there is no expectation that doses of 100 to 1000x less than used in Kovalovich will still work, especially when combined with the absence of any reasonable predictability that treatment would even be effective merely from knowledge of the effects of pre-treatment.

Accordingly, Kovalovich cannot make obvious the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 19, 21-23, 25, 28, 31, 32, 40, 41, 43-45, 48, 50, 53-55 and 57-62 have been rejected under 35 U.S.C. §103(a) as being unpatentable over WO 99/02552 (1999). This rejection is respectfully traversed.

The examiner refers to Example 8 on pages 39-40 of WO 99/02552 for its disclosure that administration of IL-6R/IL-6 chimera 1 hour before and 4 hours after CCl_4 protects against (not treats) CCl_4-induced liver injury in mice. However, the results obtained in Example 8 also show that IL-6 (rhuIL-6, the elected species), in contrast to the IL-6R/IL-6 chimera, was not effective (see lines 5-10 on page 40). Clearly, this is a specific teaching away from using IL-6. Claim 19 is now amended to specifically recite what IL-6 is fused to in the fusion protein embodiment (as supported in the present specification at page 18, lines 4-7; page 20, lines 17-31; and originally filed claims 33 and 34), thereby excluding an IL-6R/IL-6 chimera/fusion protein as taught at page 15, lines 9-15 of WO'552.

Accordingly, WO'552 cannot lead one of ordinary skill in the art to the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

As the examiner has already considered a fusion protein IL-6R/IL-6 in the §103(a) obviousness rejection immediately above, applicants request consideration of the species of fusion proteins together with IL-6 for further prosecution on the merits.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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